Germ Cell Tumours
PI GC 1 Protocol

POSG Pacific Island Workstream Clinical Members

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TREATMENT OUTLINE

6* cycles of identical treatment for all stages and histologies

Carboplatin (JM8), Etoposide, Bleomycin (JEB)

Each cycle 21 days.

* Number of cycles (*x*+2) where *x* is the number required to achieve CR. CR assessment will be assisted by ability to measure and follow appropriate tumour markers.

Total therapy duration usually no more than 6 months

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1.0 AIMS

Primary

1.1 To increase the proportion of children with Germ Cell Tumours who are cured.

Secondary

1.2 To assess the ability of Pacific Island health systems to deliver chemotherapy according to a well-recognised Germ Cell protocol.

1.3 To assess the ability of Pacific Island health systems to provide supportive care guided by protocol and shared care advice from NZ centres.

1.4 To preserve gonadal function where at all possible, as endogenous hormone production preferable to hormone replacement therapy.

2.0 RATIONALE FOR STUDY DESIGN

2.1 Children and young people in the Pacific have not enjoyed the survival of their peers in developed health systems. This has been the result of a number of factors including late or non-diagnosis, treatment toxicity on protocols considered standard in developed health systems and treatment abandonment due to expense and family dislocation. This protocol has been drawn from strategies used by New Zealand and Australian paediatricians to treat children with Germ Cell Tumours.

2.2 The protocol should be able to be delivered in its entirety in Fiji. Eligible patients in Samoa and Tonga will be referred to New Zealand for confirmation of diagnosis, staging and commencement on therapy. All patients will be repatriated for ongoing therapy.

3.0 PATIENT ELIGIBILITY

3.1 Newly diagnosed patients with Germ Cell Tumours of any age and stage are eligible. All histological types pure Germ Cell Tumours,Yolk sac(endodermal sinus)tumours/embryonal carcinoma/choriocarcinoma) or Mixed germ cell tumours (including mature and immature teratoma, dysgerminoma and seminoma) are eligible if the tumour contains at least a microscopic focus of one or more of yolk sac tumour/embryonal carcinoma or choriocarcinoma.

4.0 EXCLUSIONS

4.1 None

5.0 INITIAL EVALUATION

5.1 Complete history including family history.

5.2 Complete physical examination

5.3 Chest X-ray and abdominal ultrasound.

5.4 CT scan of affected area plus chest and abdomen (if available).

5.5 Full blood and platelet count.

5.6 Urea, creatinine, electrolytes, calcium, liver function tests

5.7 Tumour Markers- alpha fetoprotein / βHCG / Ca 125

6.0 REGISTRATION

6.1 Upon diagnosis, all patients with Germ Cell Tumours will be recorded on the unit registry.

7.0 TREATMENT

7.1 All patients with biopsy proven Germ cell Tumours (with the exception of Stage 1 Testicular tumours- refer 7.2) will receive identical therapy. After biopsy to establish diagnosis (avoiding attempts at complete resection if this will be mutilating or functionally impairing), administer chemotherapy.

7.2 Stage 1 testicular tumours that post- orchidectomy show decreasing AFP at expected rate, will receive no further treatment, unless there is a rise in the AFP or clinical recurrence.

7.3 The initial cycle of therapy should be given as soon as practically possible after appropriate supportive care has been given. This will include correction of anaemia (if applicable), treatment of infection and any co-morbidities.

7.4 First Cycle of JEB

Carboplatin	600mg/m2	iv	day 1
Etoposide	120mg/m2	iv	days 1,2,3
Bleomycin	15U/m2	iv	day 2

7.5 Second cycle of JEB starts on day 22, provided absolute neutrophil count (ANC) is >1.0 $x10^9$/L and the platelet count >100 $x10^9$/L. If these parameters are not met, chemotherapy to be withheld until count recovery. Subsequent cycles are at 21 day intervals, provided above parameters met.

At the start of each cycle check full blood and platelet count, urea, creatinine, electrolytes, calcium, liver function tests and those tumour markers that were positive at diagnosis

- alpha fetoprotein/βHCG/Ca 125

8.0 TOXICITY AND DOSE MODIFICATION

8.1 Haematological toxicity will result in delay of the subsequent course of chemotherapy rather than dose reduction. (Await recovery of neutrophil count to >1.0x10^9/L and platelets to >100x 10^9/L before giving day 1 therapy each cycle.

8.2 There are no modifications of dose for haematologic toxicity, only delays in therapy to allow for adequate recovery of neutrophil and platelet counts.

8.3 Bleomycin: If rashes or chills , or other symptoms of mild allergic reaction occur with the infusion of bleomycin, subsequent doses will be accompanied by administration of a premed (hydrocortisone and phenergan)

8.4 Etoposide: If allergic reaction occurs, subsequent doses will be preceded by a premed. If anaphylaxis with hypotension occurs, stop etoposide, give phenergan and hydrocortisone and increase IV fluids. When hypotension and signs of anaphylaxis subside, restart etoposide at half the infusion rate (give over 3 hours).

8.5 Carboplatin: Toxicity includes myelosuppression, especially thrombocytopaenia; nausea and vomiting; reversible renal toxicity and less common ototoxicity, peripheral neuropathy, hepatotoxicity, electrolyte disturbances and hypersensitivity reactions

9.0 ADMINISTRATION OF THERAPY

9.1 Etoposide and Bleomycin are irritant cytotoxics. Every care must be taken to ensure that extravasation does not occur. This will mean the establishment of reliable peripheral venous access for each chemotherapy administration and checking for vascular patency with a flush of normal saline before commencing chemotherapy administration by slow iv push or supervised infusion without the use of an infusion pump.

9.2 Bleomycin: Reconstitute to a concentration of 5units/ml with normal saline (***not*** dextrose containing solutions) and infuse over 10 minutes by

slow push. Bleomycin is stable for 24 hours at room temperature in normal saline.

9.3 Dilute Etoposide to a final concentration of <0.4mg/ml in dextrose or normal saline (usually 100mls). Infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2mg/ml. Administer over 90 minutes, after Bleomycin.

Do not administer etoposide by rapid intravenous injection.

9.4 Carboplatin in 150mls 5% dextrose over 1 hour. Administer after Etoposide.

9.5 Administer chemotherapy for sufficient cycles of chemotherapy to achieve complete remission (CR) and then 2 more. In this context, remission means absence of all evidence of disease present at diagnosis and initial staging.

CR assessment will be assisted by ability to measure and follow appropriate tumour markers. All tumour markers should be in the normal range for documentation of CR.

βHCG: N < 5 IU/L
Ca 125: N< 24 U/ml
AFP: N< 10 μg/ml (refer Appendix 1)

The half life of alpha fetoprotein is 4-7 days, so AFP levels should reduce by at least 50% each week.

9.6 If the alpha fetoprotein fails to normalise or having fallen starts to rise again, reimaging indicated, with a view to second look surgery.

10.0 COMPLETION OF THERAPY

10.1 Documentation of response including appropriate imaging (where available) will take place 1 month after the final cycle of JEB has been completed.

10.2 Follow-up to document outcome and any treatment toxicity will be documented and will form the basis of a future Germ Cell Tumour treatment strategy.

APPENDIX 1:

ALPHA FETOPROTEIN - Normal infant values

AGE	Mean AFP (μg/ml)
Premature (<37 weeks)	158,125
Newborn	41,687
Newborn- 2 weeks	33,113
2-4 weeks	9,452
1 month	2,654
2 months	323
3 months	88
4 months	74
5 months	47
6 months	13
7 months	10
8 months	9

Note: Usually by 8 months infant AFP has approached adult level